REVIEW

New dosing strategies for liposomal amphotericin B in high-risk patients

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ABSTRACT

In recent years, the focus of attention in our understanding of pharmacokinetic antifungal drug efficacy has expanded from the vascular to the tissue compartment, since for moulds in particular, this is the primary point of encounter between the invading fungus and the host. Liposomal amphotericin B (LAB) accumulates in the reticulo-endothelial system and other tissues for several weeks after systemic administration at concentrations exceeding the MICs for many pathogenic fungi. Animal models demonstrate that such tissue depots provide effective prophylaxis and even therapeutic opportunities when LAB is given in high intermittent doses. Efficacy has been shown for even a single high dose of LAB. Human studies have also confirmed retention of amphotericin B in tissues well beyond the last administered dose. Clinical evidence has begun to accrue that suggests prophylactic efficacy in high-risk patients with haematological malignancies who have received intermittent LAB. In an exploratory study of patients with persistent and protracted neutropenic fever, one dose of 10 mg/kg, followed by two doses of 5 mg/kg given on days 1, 3 and 6, respectively, appeared to be as effective as the standard regimen of 3 mg/kg/day given for a longer period. Serum kinetics suggest a large-volume deep tissue compartment for LAB. The drug also appears to accumulate in the tissue, as reflected by bone marrow concentrations. These early observations suggest the potential for intermittent high dosing of LAB for prophylaxis and management of invasive fungal infections, thus providing an alternative option to more frequent and expensive administration of LAB, and daily administration of azoles or candins. This might offer the benefits of lower treatment costs, improved patient compliance and reduced toxicity. Further clinical studies are required to confirm the feasibility of such an approach.

Keywords CAB, intermittent dosing, LAB, review, tissue concentrations

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MAJOR ANTIFUNGAL DRUGS

The major current monotherapeutic options for antifungal drug management are amphotericin B, fluconazole, voriconazole and candins. The preferred drug in terms of efficacy and safety is a matter of considerable debate, not least because of the heterogeneity of patients, endpoint definitions and interpretations encountered in the different randomised clinical trials and some incongruous findings, such as the <10% response rate for invasive aspergillosis to amphotericin B in one recent study [1]. These issues have been discussed recently [2]. Notwithstanding limitations, amphotericin B, particularly in its liposomal formulation, is at least as good an alternative drug as voriconazole and caspofungin. Liposomal amphotericin B (LAB, AmBisome®, Gilead Sciences, Sandimas, CA, USA) uniformly has fungicidal activity, causes relatively few course-terminating adverse drug events, leads to a low incidence of emergent resistant organisms and has a wide spectrum of fungal species coverage. The limited adverse event profile is superior to that of conventional amphotericin B (CAB); toxicity-related events are significantly reduced [3] and associated survival advantages have been documented [4]. One review has called for LAB as the 'new gold standard' [5]. The lipid formulation Abelcet (amphotericin B lipid complex (ABLC)) has a toxicity profile similar to CAB, indicating

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the profound differences that exist between the lipid formulations [6].

SETTING OF PROTRACTED NEUTROPENIC FEVER

The haematological patient with fever and protracted, severe neutropenia with unexplained clinical and microbiological cause of the fever is at high risk for an invasive fungal infection (IFI). Addition of CAB to the therapy for such patients, supplementing broad-spectrum antibiotic coverage, has been shown to significantly reduce overt IFI [7,8]. However, it is necessary to treat approximately ten patients to prevent one IFI event [8], amphotericin B is toxic, (LAB still carries *c.* 15% risk of nephrotoxicity) and LAB has high acquisition costs. This blunderbus approach has rightly attracted criticism [9]. However, not only does identification of that subgroup of patients involve highly intensive diagnostics, but application of existing serological methodologies requires much more clinical validation before they can be universally applied. For example, the galactomannan test is only moderately sensitive, detects only *Aspergillus* (<50% among the increasing diversity of invasive fungi encountered) and has high inter-centre variability in performance [10,11]. However, recent studies do support its use in the clinical arena [12]. β-D-Glucan detects a wider range of IFIs but is subject to false-positive findings [13,14]. PCR testing also has limitations. High-resolution computed tomography imaging of the lungs to detect the 'halo sign', a virtually pathognomonic marker for invasive pulmonary aspergillosis (IPA) in this patient population, is highly sensitive but is also expensive, and requires early and repeated examinations to be useful [15]. In the context of such diagnostic limitations, an alternative or supplementary approach is to consider alternative dosing regimens for LAB, particularly in the setting of antibiotic-unresponsive neutropenic fever (AUNF) or prophylaxis.

LIPOSOMAL AMPHOTERICIN B AND DOSE RESPONSES

LAB has unique properties that are not seen with the parent drug CAB. Doses of the order of 3–5 mg/kg/day are commonly used in clinical practice without the attendant high frequency of adverse reactions seen with CAB [3]. The unique structure of LAB, with its complex bilayer drug-encapsulating membrane, facilitates accumulation of amphotericin B at sites of fungal infection [16], where tissue phospholipases cleave amphotericin B [17], the drug then entering into macrophages and fungus-infected cells [18]. The drug is effective at relatively low doses because of this mechanism of cellular delivery. Yet there is evidence of a dose-related therapeutic effect. In a maximum-dose-finding study, dosages between 7.5 and 15 mg/kg/day were administered [19]. The frequencies of infusion-related reactions (chills, rigors, chest pain, dyspnoea), nephrotoxicity (greater than or equal to a two-fold rise in creatinine), hepatotoxicity and drug discontinuation because of toxicity were not different between the four different dosages given. The maximum tolerated dose appeared to be in excess of 15 mg/kg/day. This study suggested a pragmatic approach of high-dose administration of LAB for managing patients with an IFI progressing on lower, 'standard' doses. Animal models and in-vitro studies confirm increased efficacy in parallel with elevated doses [20,21]. Thus, Olson *et al.* (2006) demonstrated that LAB accumulated in (uninfected) murine lung tissue in a linear fashion that was dependent on dosage and number of doses administered [21] (Fig. 1a). Immunosuppressed mice, when challenged intra-nasally with *Aspergillus fumigatus* and then treated with 15 or 20 mg/kg LAB for 3 days, had a greater reduction in IFI fungal burden with the higher doses (Fig. 1b). High survival rates of up to 90% were obtained, without significant nephrotoxicity.

BLOOD COMPARTMENT KINETICS AND RESPONSES

High AUC, high C_{max} and non-linear pharmacokinetics have been well-characterised for the blood compartment in patients receiving LAB. The in-vitro concentration-dependent activity of amphotericin B indicates that maintaining blood levels above the MIC for bloodstream IFIs would be best achieved by administering high doses of the drug, at least initially. This has been shown in animal studies [22,23]. Furthermore, other antifungal drugs such as caspofungin and itraconazole are given with initial high loading doses. However, a recent clinical trial indicated that

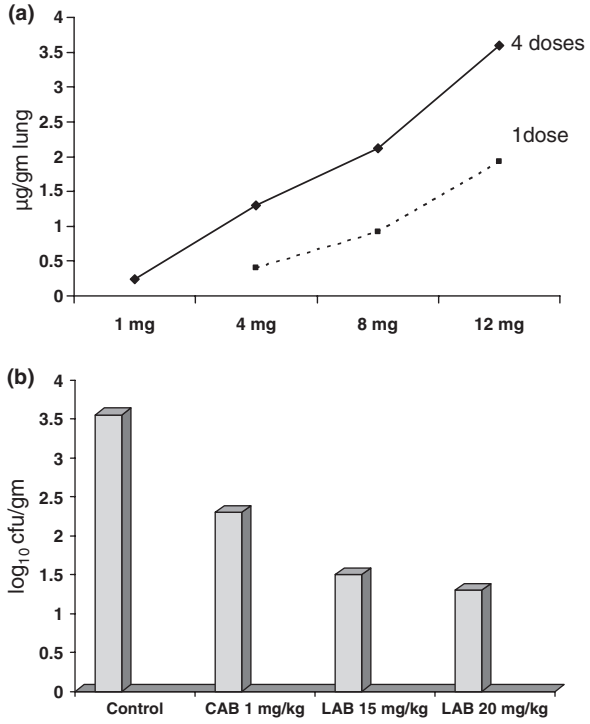

Fig. 1. (a) Amphotericin B concentration in lungs after one or four doses of LAB. (b) Fungal burden in lung tissue in mice infected with *Aspergillus fumigatus* treated for 3 days.

improved outcome in patients with IPA was not achieved with higher (10 mg/kg/day) than with lower (3 mg/kg/day) doses of LAB [24].

The traditional understanding of the efficacy of antifungal drugs has pivoted around peak plasma concentration. A concentration-dependent killing phenomenon for *Candida* has been established for CAB. Thus, higher blood C_{max}/-MIC ratios, optimally 10.0, have been found to be more therapeutically effective than strategies that maximise overall drug exposure with high AUC/MIC ratios in *Candida* infection [22,23]. Recently, this was also established for IPA, when the most effective C_{max}/MIC ratio was established as 2.4 [22].

TISSUE CONCENTRATIONS

Another property of LAB is its ability to achieve fungicidal concentrations in the reticulo-endothelial and other tissues. This is of fundamental importance in managing IFIs that have localised to the key target organs of liver, spleen, kidney, central nervous system and lung. It is clear that antifungal drug activity varies with the infected organ studied—for example, a higher dose of CAB is required to achieve the same degree of fungal burden reduction in the kidney than in the lung [23]. This observation suggests that tissue kinetics are important factors governing response. However, the IPA animal models used may not mimic the human situation [22].

Therefore, in recent years, the focus of antimycotic activity has shifted from the blood compartment to tissue sites of infection. Pragmatically, it seems that the antifungal drug concentration at actual tissue sites of fungal infection may be as important as the peripheral kinetics. This may be particularly important for those fungal infections whose primary portal of entry is extravascular, such as *Aspergillus*.

It is generally accepted that on a mg/kg basis CAB is approximately five to ten times more effective than LAB [23,24]. However, serum kinetic studies clearly show that serum exposure to LAB is substantially greater than that to CAB. The C_{max} and AUC values are 26-fold and eight-fold more with LAB, while the elimination half-life is 60% that of of CAB. This discrepancy between serum kinetics and drug activity may be explained by the more avid tissue binding that occurs with CAB (*c.* five- to ten-fold more). In addition, tissue kinetic studies demonstrate the converse of the serum profile, namely a higher tissue exposure to CAB than to LAB [23]. Thus, AUC values for CAB, as compared to LAB, are five-fold, four-fold and two-fold greater in the kidney, liver and lung, respectively. In fact, the ratio of organ LAB:CAB AUCs of effective doses is similar, at 1:1. The major potential advantage of LAB over CAB is therefore the possibility of systemically administering higher doses of amphotericin B as a liposomal formulation without substantial dose treatment discontinuations for nephrotoxicity, thus delivering higher cumulative tissue concentrations in a shorter period of time [25].

RETENTION OF AMPHOTERICIN B IN TISSUES

Another pertinent observation is that LAB is retained in tissues well beyond the final administered dose, raising the possibility of a tissue depot for amphotericin B. Human data on this are limited but clear. Seven patients who had

received LAB and 13 Amphocil for suspected/proven IFI, and who died from multi-organ failure, had amphotericin B levels measured by HPLC in specimens removed at autopsy. Tissue levels, sampled at a mean time of 16–36 h after the final dose of LAB ,varied between 11.63 mg/kg in the lung and 102.81 mg/kg in the liver. These exceeded the MIC_{90} values for most *Aspergillus* (1–2 mg/L) and *Candida* (0.25–2.0) spp.. Furthermore, the concentrations of amphotericin B in spleen, kidney, myocardium and cerebral cortex were significantly correlated with the cumulative dose of LAB given ($r \geq 0.88$, $p < 0.01$) [26]. In 18 patients with lung cancer undergoing lung resection, amphotericin B levels in the serum and lung were measured over 24 h following a 1-h single infusion of LAB 1.5 mg/kg. As the plasma amphotericin B concentration fell from 3.4 to 1.0 mg/L between the 10th and 24th hour, lung concentrations progressively increased from 1.0 to 2.5 mg/kg, confirming lung tissue accumulation of the drug [27]. Among haematological malignancy patients with IFI, three patients who died among 116 receiving LAB for IFI had autopsy specimens assayed for amphotericin B. For a mean cumulative dose of 1716 mg (820–3428), the mean lung concentration was 16.83 (0.55–45.79) mg/kg [28]. In another autopsy study, 13 cancer patients underwent tissue amphotericin B determination. Recovery in liver, spleen, lung and kidney was correlated with the total cumulative dose of CAB, and varied between 0.4 and 147.1 mg/kg tissue. The median duration between the last infusion and autopsy sampling was 27 h. Fungistatic titres were observed and linearly correlated with the amphotericin B concentration [29]. Finally, there have been some previous reports that amphotericin B can be recovered from tissues for up to 100 days following treatment completion [30].

However, there is a differential tissue distribution of amphotericin B within a particular organ, and this partly depends on the type of lipid formulation of the drug. Groll *et al.* [31] demonstrated that LAB concentrations in epithelial lining fluid were between 2.5 and five times higher than those of CAB, ABLC or amphotericin B colloidal dispersion (ABCD). However, pulmonary alveolar macrophage concentrations were similar between the amphotericin B preparations. Actual lung tissue levels for LAB were lower than those of ABLC but similar to those of ABCD and higher than those of CAB. In airborne mould infections such as IPA, the distal airways of the lung and alveoli are important first contact sites with phagocytes, and optimal tissue concentrations are therefore important. Although the observations made by Groll and colleagues are important, the therapeutic implications are currently unknown.

TISSUE RETENTION OF AMPHOTERICIN B AND RELATION TO ANTIFUNGAL EFFICACY

Prophylaxis

The knowledge that amphotericin B accumulates in the reticulo-endothelial system [32] and other tissues following its administration opens the possibility that such tissue depots might play a role in the management of IFI in a variety of settings. Several key animal studies have shown that pre-administration of LAB is highly effective in preventing IFI. Garcia *et al.* [33] challenged immunosuppressed mice with *Histoplasma capsulatum* 7 days after admistering a single dose of CAB or LAB at doses ranging from 1 to 20 mg/kg. A single dose of either 10 or 20 mg/kg LAB resulted in sterilisation of the spleen by day 10 after challenge, and 100% of the animals survived, as compared to 20% of those in the control group, which also had substantial organisms in their tissue. At day 24, however, protection from IFI had diminished, with a minority of the mice now having the same infection. Survival was 60% in the 10 mg/kg group and 80% in the 20 mg/kg group. In a subsequent experiment using *Candida albicans*, significant reductions in the kidney fungal burden were documented with LAB at all doses, as compared to the controls or to CAB treatment, and the effect was proportional to the dose of LAB used. Concentration determinations of amphotericin B in the kidney and spleen at 7 days after the single administered dose showed dose-dependent increasing accumulation of the drug (Fig. 2a,b). Similar results were obtained in immunocompetent mice. The findings therefore demonstrate that a single high dose of LAB accumulates in tissue for at least 7 days after administration, at concentrations above the MICs for most pathogenic fungi, and that this

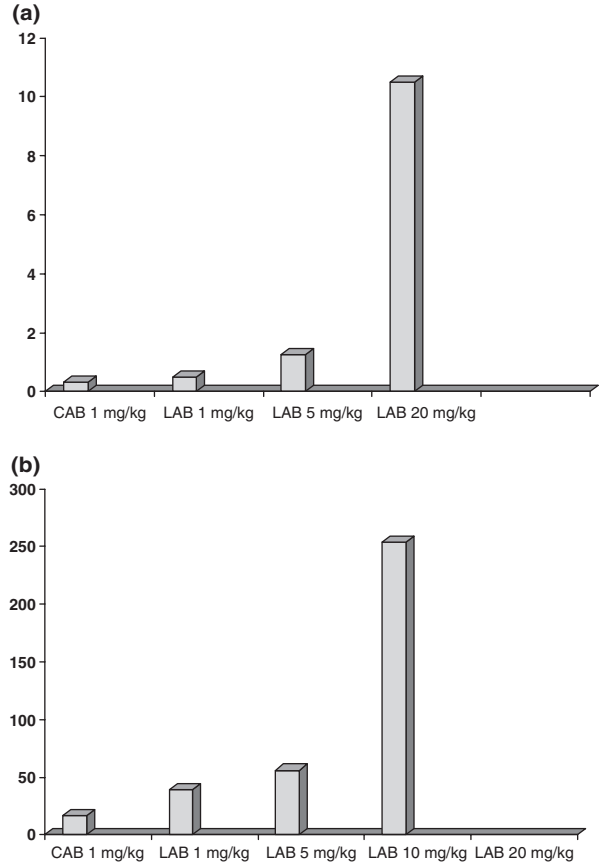

Fig. 2. (a) Concentrations of amphotericin B in kidney of immunosuppressed mice. (b) Concentrations of amphotericin B in spleen of immunosuppressed mice.

phenomenon correlates strongly with tissue antifungal activity. However, the fact that in the *Histoplasma* challenge model LAB did not result in sustained, complete elimination of the organism from the spleen reflects the importance of both host response and of selective organ penetration and accumulation of amphotericin B in determining successful eradication. This is because, in the model used, cyclophosphamide disrupts T-cell dysfunction, and hence elimination of *Histoplasma* is not possible. In the *Candida* experiment, although the IFI burden was reduced, it was not eliminated completely, since LAB localises to macrophages, whereas *Candida* replicates extracellularly. The correlation between the concentration of amphotericin B in tissue and drug prophylactic efficacy against *Histoplasma* was greater than that seen for *Candida*, probably because of the lower doses of LAB in the kidney than in the spleen.

In another experiment, mice were given LAB at either 2.4 mg/kg for 5 days per week for 5 weeks or 15 mg/kg weekly for 4 weeks [25]. Amphotericin B accumulated by rank order spleen > liver > kidney > lung. In the spleen, there was no difference in the tissue-accumulated amphotericin B between the two regimens. At 3 weeks post-treatment, there was *c.* 270–290 mg/kg amphotericin B in the spleen, and this fell to 100–115 mg/kg at 6 weeks post-treatment. Clearly, levels well in excess of fungal MICs were seen in all tissues apart from the lung, which showed undetectable levels until 3 weeks (corresponding to a 180 mg/kg cumulative dose). Reduction in tissue levels post-treatment depended on the organ; for example, no reduction between week 3 and week 6 was found in the kidney. When a *Candida glabrata* challenge was given at 1, 3 or 7 days after completion of a single dose or two doses of LAB prophylaxis, there was a significant reduction in fungal burden over all days as compared with controls. There was a dose-dependent association with the number of kidneys free of *C. glabrata*. Similar findings were seen with a *C. albicans* challenge. At both 3 and 6 weeks post-treatment, a significant drop in CFU in the kidney was found, with no difference between the regular daily or intermittent dosing schedules. In the spleen, there was a significant fall in fungal burden at 3 weeks with intermittent dosing as compared to daily dosing, but not for the 6-week time-point. Both regimens demonstrated significant drops in CFU. These experiments support the notion that high intermittent dosing with LAB produces substantial, sustained tissue (variable, depending on organ) accumulation of amphotericin B, which has substantial antifungal activity during subsequent fungal challenge. (Fig. 3a,b).

Treatment

Evidence has also emerged that intermittent dosing is as effective as regular daily dosing in the definitive treatment of IFI. In a study of immunocompromised mice infected intravenously on day 2 with *Candida* and then given variable doses of LAB intermittently, the following sentinel observations were made [34]. A higher cumulative dose given over the first 4 days was more effective than a lower cumulative dose given daily. The experiment showed that the

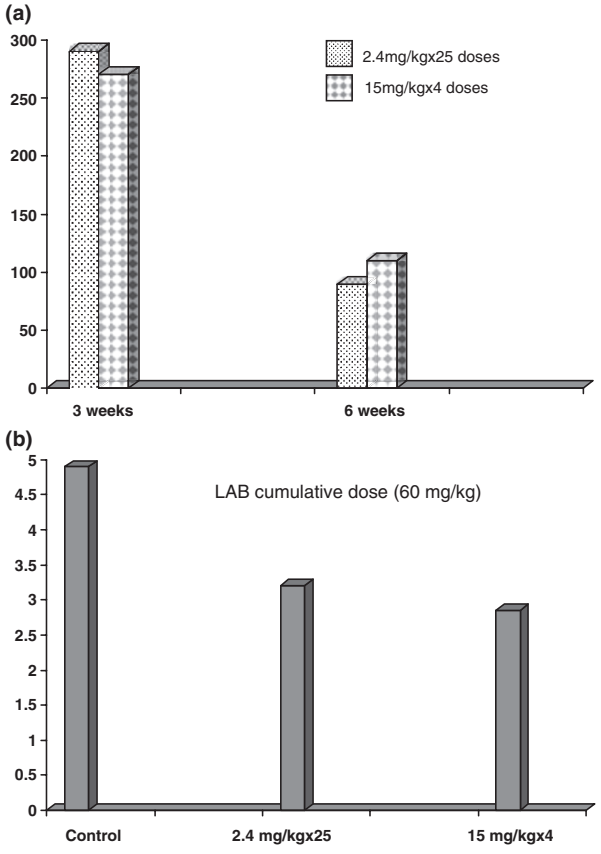

Fig. 3. (a) Amphotericin B concentration in spleen. (b) Log_{10} CFU/g kidney at 6 weeks post-treatment.

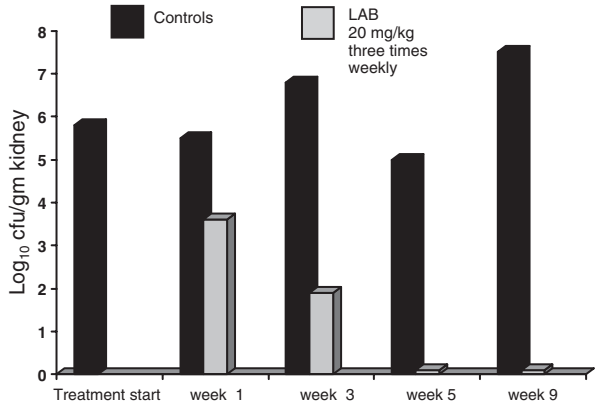

Fig. 4. Fungal burden in kidney.

efficacy of treating an IFI can be sustained even when the frequency of dosing of LAB is reduced from the standard traditional approach of once-daily. Even a single high dose of LAB was as effective as daily dosing in reducing IFI. Furthermore, the therapeutic efficacy of such an intermittent dosing approach is increased when the doses administered are higher, at 20 mg/kg, and particularly when the total cumulative dose increases—after 5 weeks of intermittent high-dose treatment with 20 mg/kg (cumulative 300 mg/kg), the tissues examined are sterile as compared to controls, in which log_{10} 7.5 CFU are found (Fig. 4).

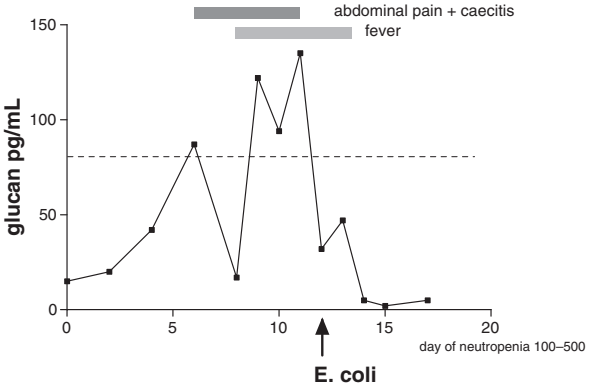

Fig. 5. High β-D-glucan levels in a patient without invasive fungal infection .

HUMAN STUDIES

Kinetics and safety

Several human studies have also investigated intermittent dosing, and have supported the feasibility of an intermittent dosing approach to prophylaxis and treatment. This may be particularly relevant in the setting of AUNF, due to cryptic IFI, where the fungal burden will, by definition, be low, but the possibility of low-density fungal dissemination might be presumed. The occurrence of glucanaemia without overt IFI in patients with severe entero-mucositis supports this (Ellis, unpublished data; Fig. 5). The administration of intermittent amphotericin B in such patients might provide an alternative management option while simultaneously reducing total drug exposure and thereby limiting nephrotoxicity, other adverse reactions and costs.

A safety study concentrated particularly on at-risk patients—those receiving reduced-intensity conditioning allogeneic stem-cell transplantation [35]. They received high-dose (7.5 mg/kg) weekly LAB prophylaxis. Twenty-nine per cent of 21 patients had infusion-related reactions, and 33% of patients had treatment discontinued because of

severe reactions, including creatinine rise >1.5 times baseline, hypotension and violent chest pain—all of which resolved spontaneously. The median percentage variation in serum creatinine over the LAB administration period was 15% ± 12%. Despite the notable adverse reactions, the data did provide support for undertaking an efficacy study.

The study of Mehta *et al*. generated important but limited paediatric data [36]. This was a kinetics study in which 10 mg/kg LAB was given weekly to 14 children undergoing stem-cell transplantation for unusual congenital abnormalities such as severe combined immunodeficiency or Fanconi's anaemia. There were no significant adverse changes in creatinine, potassium, magnesium or liver enzymes. This is in keeping with paediatric experience for other polyene formulations. One week after the first infusion and after the fourth weekly infusion, the plasma concentrations remained around the MICs for most susceptible strains of *Candida* and *Aspergillus* spp. that are likely to be encountered. The data support the feasibility of administering weekly high-dose LAB safely to children as an alternative antifungal strategy to long-term azole prophylaxis, which carries the risk of liver toxicity, or caspofungin, which needs daily administration.

Another human safety study was performed by Cordonier and colleagues [37]. A single weekly high dose (10 mg/kg) of LAB was given to 15 patients undergoing first induction chemotherapy or 15 patients undergoing dose consolidation chemotherapy or allogeneic stem-cell transplantation (for 8–12 weeks, depending on the presence of acute graft vs. host disease). Five of 23 patients (21.7%) had infusion-related reactions, and 7/23 (30.4%) had rises in creatinine >1.5 times baseline. Treatment was discontinued in five of eight patients (62.5%) in the transplant group because of toxicity. Although efficacy was not a primary outcome, it was mentioned that fever of unknown origin occurred in *c*. half of all patients, and an IFI in 17%. The timing of the LAB prophylaxis in the transplant group remains to be determined.

Feasibility and efficacy

An early study was that of Kelsey *et al*. [38]. In a randomised, blinded, placebo-controlled clinical trial, LAB at 2 mg/kg three-times-weekly as prophylaxis, from the start of chemotherapy until neutropenia resolution, was compared to placebo. Among 161 patients studied, a proven IFI developed in only 3/87 patients—all on placebo. However, suspected IFI, defined as AUNF, occurred in 31/74 patients receiving LAB (41.9%) vs. 40/87 receiving placebo (46%) (difference not significant). Fungal colonisation in the LAB arm was half that in the placebo arm (15/74 (20.2%) vs. 35/87 (40.2%)) ($p < 0.01$). The failure of this study to show a significant protective effect of LAB was due to the overall low incidence of IFI, small sample size, lack of modern fungal diagnostics and an inappropriate definition for suspected IFI.

A neutropenic study compared LAB with no systemic prophylaxis in patients who had expected severe and protracted neutropenia resulting from chemotherapy or who had undergone autologous stem-cell transplantation [39]. LAB was administered at a low dose of 50 mg on alternate days. The European Organisation for Research and Treatment of Cancer/mycoses study group (MSG) criteria were used to identify prophylaxis failures. The group receiving LAB had significantly fewer IFIs (particularly IPA) overall (5/75–6.7% vs. 20/57–35%, p 0.001). Secondary endpoints indicated a significant reduction in idiopathic pneumonia (5.5% vs. 25.7%) as well as superficial fungal infections and use of antifungal treatment. Crude and IFI-related mortalities were reduced, but not significantly (1.8% vs. 7.3%, p 0.07). The trial was limited by its open design and bias from multiple patient re-entry. However, the same degree of difference was observed when analysis was confined to first neutropenic event.

The final study is this authors' work. The design was a randomised clinical exploratory trial in which patients received either standard treatment (arm B) (3 mg/kg/day) or intermittent high dosage (arm A) (10 mg/kg day 1, 5 mg/kg days 3 and 6) of LAB for AUNF. This feasibility study addressed broad safety and efficacy trends and collected data on kinetics. With use of a five-point composite score, the success rates were 67% and 66%, respectively. Similar specific failure incidents occurred in each arm (Table 1). One death was documented in arm A, due to a combination of resistant haematological disease and extensive progressive IPA present at baseline. Days to defervescence were similar. The proportions of patients who developed serology positive

Table 1. Efficacy

	3 mg/kg/day (Arm B)	10, 5, 5 mg/kg (Arm A)
Enrolled, *n*	15	15
Success of ITT	10/15 (67%)	10/15 (67%)
Failure of baseline IFI to respond	0	0
Failure to defervesce	1	2
Discontinuation of treatment	1	2[c]
Breakthrough IFI	3[d]	0
Death	0	1[e]
Success of modified ITT	13/14 (93%)[a]	11/14 (79%)[b]
Days to defervescence	8.4 ± 6.1 (2–20)	8.8 ± 5.1 (2–19)
Patients developing positive serology	3/11 (27%)	4/14 (28%)

ITT, intention to treat; IFI, invasive fungal infection.
[a]Neutropenia resolved at day of study entry.
[b]One patient with extensive probable IPA diagnosed after study entry.
[c]Given other antifungals because of defervescence failure.
[d]Two probable + one possible IPA.
[e]Probable IPA (same patient as in b).

Table 2. Comparison of population pharmacokinetic parameters from the two arms

	Arm A			Arm B		
	Population mean estimate	SE[a] (% CV)	Inter-individual variability[b] (% CV)	Population mean estimate	SE[a] (% CV)	Inter-individual variability[b] (% CV)
Age (years)	36.3 ± 14			36 ± 11		
Weight (kg)	66.5 ± 16			66.3 ± 17.5		
V1 (L)	258	11.24	32.09	6.17	30.31	126.1
V2 (L)	3100	47.74	31.16	157	6.62	14.56
Clearance (L/h)	2.46	23.37	56.92	4.72	10.74	23.15
Total AUC (mg·h/L) (±SD)	236 ± 64.7			541 ± 163		
Total AmBisome dose (mg) (±SD)	1328 ± 358			2732 ± 723		
AUC drug dose normalised (mg·h/L/mg)	0.178			0.198		

V1, central compartments; V2, peripheral compartments.
[a]Coefficient of variation of the estimates (100 × SE estimate/estimate).
[b]Estimates of variability expressed as approximate percentage coefficient of variation (% CV, 100 $\sqrt{\Omega}$).

for an IFI were also similar in both arms. The mean changes in serum creatinine concentrations were also similar in the two study arms. Frequencies of adverse drug events were 40% in arm B and 47% in arm A, although there were rather more patients in arm A with infusion-related chills or rigors (40% vs. 27%). However, treatment was not discontinued for any patient in either dosing schedule because of toxicity. Blood was sampled over selected days, and times of LAB infusion and bone marrow were sampled after the last infusion was completed, for bioassay of amphotericin B. Using a two-compartment model to fit the serum–time concentrations, the

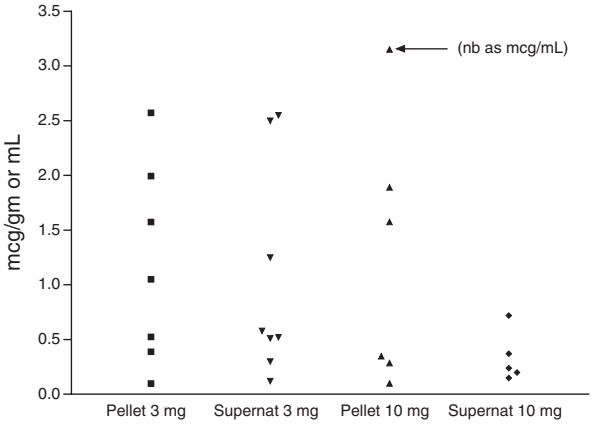

Fig. 6. Bone marrow concentrations of amphotericin B.

central and peripheral compartments were strikingly larger than in previously published studies (Table 2). This may be partially explained by the prolonged sampling time of 400 h, and the high peripheral compartments (V2) may indicate a deep compartment for the drug. Clearance and AUC parameters were lower in arm A, but when the figures were normalised for total LAB given, they were similar. The reduced total serum exposure of the drug in arm A offers the possibility of reduced toxicity. Amphotericin B concentrations in the bone marrow varied widely among patients (Fig. 6). However, antifungal activity could still be detected in the marrow for up to 7 days after the last infusion in arm A. Values as high as 3.2 mg/L were documented. The study confirms the feasibility of administering high initial and then intermittent doses of LAB safely to patients with haematological malignancy undergoing chemotherapy and who develop AUNF. These initial, limited data suggest that such an approach may provide similar efficacy as a more standard dosing regimen but with substantial savings in drug costs and administration. This hypothesis should be tested in a larger clinical trial.

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